2. RESPONSE

2.1 STATUS OF THE CLAIMS:

Claims 1-30 were pending at the time of the Action.

Claims 13-20 were withdrawn without prejudice and without disclaimer, as being directed to non-elected inventions.

Applicants elected to prosecute the subject matter of the Group I invention.

Claims 1-3, 7, 12, and 25 were amended herein.

Claims 31-40 were added herein.

Claims 1-12 and 21-40 are now pending in the case.

Applicants note for the record that all pending claims were free of rejection under 35 U. S. C. §§ 102, and 112, 2nd paragraph, and appreciate the Examiner's finding that the claimed subject matter is novel and definite. The objections to claims 1, 11, and 30, the single rejection of claim 29 under 35 U. S. C. § 101, and the enablement and prior art rejections under 35 U. S. C. §§ 112, 1st paragraph, and 103 are each addressed in the remarks that follow.

Applicants respectfully request reconsideration of the remarks herein, removal of all outstanding claim objections and rejections, and allowance of all pending claims.

2.2 THE ATTORNEY DOCKET NUMBER FOR THIS CASE HAS CHANGED

As noted in Applicants' previous response, the undersigned representative relocated his practice from Customer No. 23720 to Customer No. 27683. **The new attorney docket number for this case is: 36689.26.**

Applicants appreciate the Examiner's so noting of this in all subsequent communication with the undersigned representative, and that the attorney docket number for this file be corrected to reflect this change.

2.3 SUPPORT FOR THE CLAIMS

Support for the pending claims can be found throughout the original claims, specification and figures as filed. It will be understood that no new matter is included within any of the newly-added or amended claims.

2.4 THE OBJECTIONS TO CLAIMS 1 AND 30 ARE IMPROPER.

The Action at page 2 objected to claims 1 and 30 as allegedly because "it is noted that the 'instructions' are a physical component of the claimed kit, but are not patentable because they are not functionally related to the instant polypeptide".

Applicants respectfully traverse.

With respect to claim 1, Applicants are perplexed by the Examiner's reasoning that the claim should be objected to, particularly since the claim is directed to "a composition" and not "a kit." In fact, the claim does not even *contain* the words "kit" or "instructions." This objection is therefore utterly without foundation. As such, Applicants respectfully request that the objection to claim 1 be immediately withdrawn.

With respect to claim 30, Applicants are likewise mystified by the Examiner's reasoning that the claim should be objected to because the claimed kit allegedly is not patentable because the instructions contained within the kit are "not functionally related to the instant polypeptide." First, there is no requirement under U.S. law of which the Applicants are aware that require that all elements of a claim be "functionally related." Second, the US patent literature is replete with issued patents with claims directed to embodiments in which there is no "functional relationship" between all of the claimed elements. Moreover, in the biotechnological arts, there are literally

hundreds of U.S. patents issued in the past 10 years that contain the exact same, or equivalent claim language as that objected to in the instant case.

As the Examiner appears to be unfamiliar with this claim language, Applicants have performed a database search and identified a number of US patents that have issued from TC1600 in which this exact claim language currently objected to is found.

For example, in US Patent 6,946,274, claim 1 is directed to "An isolated nucleic acid molecule," and claim 9 recites "A *kit* comprising the molecule of claim 1 and *instructions* for use."

In US Patent 6,989,144, claim 2 is directed to "A antibody or antigen binding portion thereof...." Claim 13 of the same patent recites: "13. A *kit* comprising the antibody or antigen binding portion thereof of claim 2 and *instructions for use.*"

In US Patent 7,001,753, claim 1 is directed to "An isolated nucleic acid molecule," while claim 9 recites "A *kit* comprising the nucleic acid molecule of claim 1, and *instructions for use.*
In US Patent 6,924,264, claim 1 is directed to "(a) polymer-modified exendin or agonist analog of an exendin....." Claim 22 recites " A *kit* comprising a polymer-modified exendin or agonist analog of an exendin of claim 1 and *instructions for use* or packaging for use."

Similarly, in US Patent 6,900,032, claim 6 is directed to "(a)n isolated polypeptide, comprising an amino acid sequence consisting of SEQ ID NO:4." Claim 10 recites "A *kit,* comprising the polypeptide of claim 6; and *instructions for its use* in the detection of anti-PTTG antibody in a sample."

Likewise, in US Patent 6,821,514, claim 1 is directed to "(a) composition for reducing symptoms of autism in a human patient...." Claim 22 of the same patent recites "A *kit*

comprising a vessel containing a composition according to claim 1, and *instructions directing the use* of the composition to reduce the symptoms of autism in a human patient."

In US Patent 6,911,335, claim 1 is directed to "(a)n isolated nucleic acid molecule...." Claim 13 recites "A *kit* comprising a compound which selectively hybridizes to a nucleic acid molecule of claim 1 and *instructions for use*."

Likewise, in US Patent 6,864,078, claims 1 to 4 are directed to "(a)n isolated nucleic acid molecule....." Dependent claim 11 recites "(a) *kit* comprising the nucleic acid molecule of any one of claims 1, 2, 3, or 4 and *instructions for use*."

As the Office has provided no foundation for this objection in the law, and further that numerous patents have been issued from TC1600 which contain precisely the same language as that which has been objected to in the present case, Applicants respectfully request that the objection to claim 30 be withdrawn.

If such an objection is maintained in the next Action, however, Applicants respectfully request that the Examiner identify specific portions of the Statutes and/or Code which state that there must be a "functional relationship" between "all elements within a claim", and provide Applicants with an explanation as to why, if such a statutory requirement exists, that the exact same claim language has been found permissible in hundreds of US Patents issued in the biotechnological and chemical arts in the past decade.

2.5 THE OBJECTION TO CLAIM 11 IS IMPROPER.

The Action at page 2 also objected to claim 11 under 37 C. F. R. § 1.75(c) allegedly as being in improper dependent form for failing to further limit the subject matter of the previous claim.

Applicants respectfully traverse.

Pending claim 1 is directed to "A composition comprising an adeno-associated viral vector that comprises a nucleic acid segment encoding a pro-opiomelanocortin polypeptide operably linked to a promoter capable of expressing said segment in a host cell that comprises said vector....."

Pending claim 11 recites "The composition of claim 1, comprised within a kit for diagnosing, preventing, treating or ameliorating the symptoms of a pro-opiomelanocortin polypeptide deficiency condition in a mammal." (emphasis added)

Applicants are puzzled why the Office has taken the position that claim 11 does not further limit claim 1. There is no limitation in claim 1 that its composition be comprised within *any* particular article of manufacture. In contrast, however, claim 11 clearly further limits the scope of claim 1, by specifying that the claimed composition be *comprised within a kit for diagnosing, preventing, treating or ameliorating the symptoms of a pro-opiomelanocortin polypeptide deficiency condition in a mammal.* This limitation is clearly proper.

Turning again to existing US patents issued from TC1600 as evidence that the objected to claim language is widely used in the biotechnological arts, the Examiner is invited to examine US Patent 6,514,747 in which claim 2 recites, "The isolated polynucleotide of claim 1....." In this patent, claim 32 depends from, and further limits, claim 2 by reciting: "(t)he polynucleotide of claim 2, *comprised within a vector*."

Likewise in US Patent 6,326,129. claim 1 is directed to "An isolated polynucleotide segment....." Dependent claim 4 recites "(t)he polynucleotide of claim 1, *comprised within a vector.*" Similarly, in US Patent 6,017,734, claim 1 is directed to "A nucleic acid segment comprising at least a first sequence region that encodes a targeting polypeptide....." Dependent claim 41 recites "(t)he nucleic acid segment of claim 1, *comprised within a host cell.*"

In the instant case, as claim 11 clearly, unambiguously, and properly further limits claim 1, by requiring the limitation "comprised within a kit for diagnosing, preventing, treating or ameliorating the symptoms of a pro-opiomelanocortin polypeptide deficiency condition in a mammal,"

As such, and in light of the evidence of this language in many other recently-issued US Patents from the same art unit, Applicants assert that the objection is improper and respectfully request that it be withdrawn.

2.6 THE REJECTION OF CLAIM 29 UNDER 35 U. S. C. §101 IS IMPROPER.

The Action at page 3 rejected claim 29 under 35 U. S. C. § 101, allegedly as being directed to non-statutory subject matter.

The Office states that "claim 29 as written, does not sufficiently distinguish over nucleic acids, proteins, cells, and antibodies as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally-occurring products" The Examiner suggests that the claims should be amended to "indicate the hand of the inventor, *e.g.*, by insertion of isolated or purified."

Applicants respectfully traverse.

According to the Statutes, "the subject matter of the invention or discovery must come within the boundaries set forth by 35 U. S. C. § 101, which permits patents to be granted only for

"any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof." M. P. E. P. § 2105 devotes significant explanation to what is patentable in view of several court cases bearing on utility.

In the landmark Supreme Court case *Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980) the court cited *Funk Seed Co. & Kalo Co.*, (333 U.S.127,1948), and stated "(H)ere, by contrast, the patentee has produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility. His discovery is not nature's handiwork, but his own; accordingly it is patentable subject matter under §101."

Bearing these holdings in mind, in the instant case, it is unclear to Applicants why the Office believes that a claim reciting "A mammalian host cell comprising the composition of claim 1," does not "distinguish over nucleic acids, proteins, cells and antibodies as they exist naturally," particularly wherein the "composition of claim 1" comprises a recombinantly-engineered genetic viral vector that comprises a promoter and a heterologous DNA sequence that encodes a mammalian polypeptide. This invention is *clearly* a product of human ingenuity and invention, and Applicants need not be required to further limit the claim by amendment "to indicate the hand of the inventor, *e.g.*, by insertion of the word "isolated" or "purified."

Claim 29 is directed to a mammalian host cell that comprises a recombinant adeno-associated viral vector that has been "engineered by the hand of man" to comprise a DNA segment that encodes a mammalian POMC polypeptide. This clearly "distinguishes over nucleic acids, proteins, cells, and antibodies as they exist *naturally*."

Applicants are not aware of any naturally-occurring mammalian host cells that "naturally" comprise a recombinant viral vector that has been genetically engineered to comprise non-rAAV enhancer(s), non-rAAV promoter(s), non-rAAV regulatory element(s), and certainly

none that contain a genetically-engineered DNA segment that encodes a mammalian POMC polypeptide. If, however, the Examiner has personal knowledge of such naturally-occurring mammalian host cells that comprise the claimed rAAV vector compositions, Applicants respectfully request that the Examiner follow the procedure outlined in 37 C. F. R. §1.104(d)(2), which provides (in pertinent part) that a Patent Office employee must provide an affidavit supporting such statements:

> (2) When a rejection in an application is based on facts within the personal knowledge of an employee of the Office, the data shall be as specific as possible, and the reference must be supported, when called for by the applicant, by the affidavit of such employee, and such affidavit shall be subject to contradiction or explanation by the affidavits of the applicant and other persons.

In the alternative, should the Examiner not be prepared to execute such an affidavit or to provide additional documentary evidence of such naturally-occurring host cells, Applicants respectfully request that the rejection be withdrawn.

2.7 THE REJECTION OF ALL CLAIMS UNDER 35 U. S. C. §112, 1ST PAR., IS OVERCOME.

The Action at page 3 rejected all claims under 35 U. S. C. § 112, 1st paragraph, allegedly because the Specification "while being enabling for intracerebrally microinjected pro-opiomelanocortin peptides in AAV vectors that can potentially activate melanocortin activity in rats, does not reasonably provide enablement for other methods of vector delivery (for example intramuscular) and prevention and treatment of a pro-opiomelancortin (sic) polypeptide deficiency in humans."

Applicants respectfully traverse.

The Action appears to reject the pending composition claims due to a alleged lack of nexus between the examples provided in the form of both *in vitro* activity and *in vivo* animal model data

and the "ultimate" use of the various compositions and pharmaceutical formulations and kits comprising them in one or more therapeutic regiments in the treatment of humans.

The Action on page 5 states "The Specification also includes only five examples where the compound was administered to obese Zucker rats through intracerebroventricular microinjection with promising results, but lacked any human or other mammal models as recited in the claims."

Applicants respectfully traverse.

First, there is no requirement under the law that the Specification enable *all* practical uses of the disclosed compositions. In fact, the standard for determining whether a prima facie case exists is to question whether or not the Specification enables a credible and substantial utility for the claimed invention. All that is required to enable the claimed invention is an objective teaching concerning the generation of the instant POMC-encoding polynucleotide compositions, rAAV vectors, virus, host cells, and kits comprising these compositions, and specific guidance concerning how to "make and use" the claimed compositions in a substantial, credible way.

The present Action clearly admits that the Specification enables the *in vivo* use of the disclosed rAAV-POMC compositions in the obese Zucker rat animal model. The claimed compositions have been demonstrated to be effective in this approved *in vivo* animal model, and this result, *by itself,* is sufficient to enable the claimed compositions.

Even still, the claimed compositions have *also* been demonstrated to be effective in the *in vitro* expression of rAAV vector-mediated POMC polypeptide expression. That finding, too, *by itself* provides enablement of a clear, substantial, and credible utility. That the rAAV-POMC vectors are themselves fully enabled, claims directed to host cells, pharmaceutical formulations, kits, and anything else that *comprise* such novel, useful, and non-obvious viral constructs, are also *de facto* enabled. As such, all pending claims should be free from rejection under this section of the

Statute. The requirement of providing a substantial and credible utility has been met. Applicants need not provide all *possible* utilities to satisfy the "use" requirement, nor need they *enable* all possible utilities of the claimed compositions.

Applicants respectfully submit that these assertions of non-enablement by the Examiner are unfounded both in the law, and objectively in consideration of the teaching provided by the specification regarding all aspects of the claimed invention. Therefore, Applicants earnestly request that the enablement rejection against the pending composition, host cell, virus, vector, and kit claims be withdrawn and that the application be placed in condition for immediate allowance.

2.7.1 THE SPECIFICATION NEED NOT PROVIDE HUMAN TEST DATA.

In attempting to establish a *prima facie* case to support the § 112 rejection of the pending composition, vector, viral, and host cell claims, the Action doubts whether the claimed compositions are sufficiently enabled to allow those of ordinary skill in the art to practice gene therapy on humans. This rejection under § 112, as applied against the claimed compositions is misplaced and incorrect. It has long been established that composition claims are enabled by defining any practical use of the claimed compound. *In re Nelson*, 126 USPQ 242 (C.C.P.A. 1960); *Cross v. Iizuka*, 224 USPQ 739 (Fed. Cir. 1995). The specification need not provide exhaustive clinical data (either on animals or humans) to enable how to make and use the claimed invention.

In an important case concerning rejections under 35 U. S. C. § 112, 1st paragraph, the Federal Circuit overturned the outstanding § 112, first paragraph rejections, admonishing the P.T.O. for confusing "the requirements under the law for obtaining a patent with the requirements for

obtaining government approval to market a particular drug for human consumption". *In re Brana*, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago. 34 U.S.P.Q.2d at 1439; emphasis added.

The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer. In view of all the foregoing, we conclude that applicants' disclosure complies with the requirements of 35 U.S.C. § 112 ¶ 1.34 U.S.P.Q.2d at 1442-1443; citations omitted. All that is required to comply with § 112, first paragraph, is for the specification to teach how to make and use the claimed invention so that it may be practiced without undue experimentation. *In re Borkowski and Van Venrooy*, 164 USPQ 642 (C.C.P.A. 1970).

In light of the successful animal data as detailed in the specification (and acknowledged by the Examiner on page 5 of the Action), the enablement rejection as applied against the pending composition, host cell, and kit claims is improper. With respect to the claimed compositions, the Office has not provided evidence showing that one of ordinary skill in the art would reasonably doubt the direction in the specification concerning the various uses of the claimed vectors, viral particles and cells of the present invention, or that the *in vivo* animal model data would not be predictive of *in vivo* results in humans. Simply stated, a sufficient *prima facie*

case of deficient teaching has not been established, and the burden has not been properly shifted to the Applicants to provide rebuttal evidence.

The Action appears to be requiring the presence of a working example demonstrating clinical effectiveness *in humans* for the claimed invention. The Action appears to overlook the working animal model examples and objective teachings of the specification and instead fault the Specification for failing to provide clinical results in humans. Clearly, this is an improper standard that is not supported by the case law.

In fact, rather than requiring the presence of a working example demonstrating clinical effectiveness for each species within a claimed invention, as apparently required by the instant Action, it is well established that the specification does not even have to include any working examples. M. P. E. P. §2165.01 states this with particular clarity:

> There is no statutory requirement for the disclosure of a specific example. A patent specification is not intended nor required to be a production specification. *In re Gay*, 309 F.2d 768, 135 USPQ 311 (C.C.P.A. 1962).

All that is required to comply with § 112, first paragraph, is for the specification to teach how to make and use the claimed invention so that it may be practiced without undue experimentation. In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (C.C.P.A. 1976). The need for some experimentation does not render the claimed invention unpatentable under 35 U.S.C. § 112, first paragraph. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ 2d 1016 (Fed. Cir. 1991). As a matter of law, it is also well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

The specification provides more than adequate teaching on how to make rAAV-based vectors comprising polynucleotides that encode a mammalian POMC polypeptide. The Specification demonstrates a credible and substantial utility for the claimed compositions both *in vitro*, and also *in vivo* in an acceptable animal rodent model of disease. Applicants assert that this is sufficient to enable the claimed invention, and as such, respectfully requests that the rejection be withdrawn.

2.8 THE REJECTION OF CLAIMS UNDER 35 U. S. C. §103 IS OVERCOME.

The Action at page 6 rejected claims 1-7, 11, 12, 21, 24, and 26-30 under 35 U. S. C. §103(a), allegedly as being legally obvious in view of Pritchard* et al., *(J. Endocrinol., 172:411-42, 2003)(hereinafter, "Pritchard") when taken together with Paterna* et al., *(Methods, 28:208-218, 2002) (hereinafter "Paterna").

The Action at page 8 rejected claims 1-9, 21, 26 and 27 under 35 U. S. C. §103(a), allegedly as being legally obvious in view of Pritchard* and *Paterna further in view of Lasic (Tibtech, 16:307-321, 1998) (hereinafter "Lasic").

The Action at page 9 rejected claims 1-7, 11, 12, 21-24, 26-28 and 30 under 35 U. S. C. §103(a), allegedly as being legally obvious in view of Pritchard* and *Paterna further in view of Keir* et al. *(Exp. Neurol. 160:313-316, 1999) (hereinafter "Keir").

The Action at page 10 rejected claims 1-8, 11, 12, 21-24, 26-28 and 30 under 35 U. S. C. §103(a), allegedly as being legally obvious in view of Pritchard* and *Paterna further in view of U.S. Patent 6,156,303 to Russell et al. (hereinafter "Russell").

In each such rejection, Applicants respectfully traverse.

A finding of obviousness under 35 U. S. C. § 103 requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. John Deere Co.*, 148 USPQ 459 (U.S. S.Ct. 1966).

The relevant inquiry is whether the prior art suggests the invention and whether the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 7 USPQ 2d 1673 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success *must be founded in the prior art* and not in the Applicant's disclosure (emphasis added) *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

Thus, for the cited combination of references to render the present claims legally obvious under 35 U. S. C. § 103, the references must suggest the particular claimed recombinant AAV vectors, AAV virions, as well as transformed host cells, pluralities of viral particles, compositions, and kits that comprise one or more of the disclosed rAAV vectors and/or virions. Moreover, the combination must provide one of ordinary skill in the art with a reasonable expectation of obtaining such rAAV vectors, as well as viral particles, mammalian host cells, and diagnostic and therapeutic kits that comprise such rAAV vectors.

The combination of cited references, alone or in combination with one or more of the secondary references characterized by the Action, cannot legally obviate the claimed invention when the references fail to provide the required suggestion or reasonable expectation of success of generating the disclosed AAV vectors, virions, and compositions, host cells, and/or compositions comprising them.

2.8.1 PRITCHARD DOES NOT TEACH OR SUGGEST RAAV VECTORS OR THEIR USE

On page 7 of the Action, the Office states that "Pritchard et al. teaches the use of MHC4, a mammalian POMC peptide that plays a role in the melanocortin pathway in the hypothalamus...Pritchard et al. also teaches the importance of the POMC-derived peptides as a

potential research focus: "It is becoming increasingly clear that many POMC-derived peptides and precursors are secreted in the hypothalamus and can activate melanocortin receptors."

Importantly though, the Action continues by correctly recognizing that "Pritchard does not teach the use of recombinant adeno-associated vectors." This is the key fact overlooked by the Office when considering that Pritchard and Paterna are properly combinable to form the basis for a finding of legal obviousness of the claimed invention.

In fact, Pritchard does not mention any type of viral vector compositions, and certainly no AAV-based viral vector compositions. Likewise. Pritchard does not describe the construction of rAAV viral particles, or even mention any mammalian host cells or diagnostic or therapeutic kits that comprise rAAV-based vectors that express mammalian POMC-derived peptides or polypeptides.

Based upon the Examiner's own admission, Pritchard at best vaguely "discusses the importance of the POMC-derived peptides as a potential research focus." The reference clearly fails to provide the relevant teaching, suggestion, expectation of success, and motivation to combine with Paterna to render obvious the claimed invention.

As such, Applicants respectfully request that the rejection be withdrawn.

2.8.2 PATERNA IS NOT AVAILABLE UNDER §102(B)

For a reference to be properly cited under §103(a), the reference must be available for citation under at least one provision of §102. Applicants note for the record that the present application claims priority to U.S. Provisional Patent Application Serial No. 60/462,496 which was filed April 11, 2003.

The Paterna reference was published in October 2002, less than a year before the filing of Applicants' priority application. Therefore, Paterna is only available under §102(a). 37 C. F. R. §1.131 provides that a prior art reference citable only under §102(a) may be removed

by a declaration showing invention by Applicants prior to the effective date of the reference. The rule states (in pertinent part):

> When any claim of an application or a patent under reexamination is rejected, the inventor of the subject matter of the rejected claim, the owner of the patent under reexamination, or the party qualified under §§ 1.42, 1.43, or 1.47, may submit an appropriate oath or declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference or activity on which the rejection is based.

As such, should a rejection be advanced in a subsequent Action, Applicants note that the patent may be removed as prior art through the submission of an antedating affidavit under 37 C. F. R. 1.131. Applicants specifically reserve the right to submit such a declaration in that instance.

That the Applicants have chosen in the instant paper to respond to the rejection on scientific and/or legal grounds, to even more clearly distinguish the claimed invention over the cited reference, such action is not to be interpreted as an acquiescence that Paterna truly qualifies as prior art, or that the reference may not at a later opportunity be removed by the filing of an antedating affidavit.

Applicants note that the removal of Paterna as a reference will render all current obviousness rejections moot, as Paterna forms a basis for each rejection.

2.8.3 PATERNA DOES NOT TEACH OR SUGGEST POMC-DERIVED PEPTIDES, POLYPEPTIDES, OR DNA SEQUENCES ENCODING THEM

On page 7 of the Action, the Office states that

> "Paterna et al. teaches the use of recombinant adeno-associated vectors and virions as a means for gene therapy, expression and delivery using transcriptional regulatory elements, cytomegalovirus enhancers/chicken beta-actin promoters, in compositions and kits for transfection into host cells."

The Action continues:

> "one of ordinary skill in the art at the time the invention was made would have been motivated to combine the POMC peptide of Pritchard et al and the adeno-associated viral vector of Paterna et al. because Paterna et al. teaches a method to package and deliver specific genes.

Applicants respectfully disagree.

Paterna, in fact, does not teach or even mention any polynucleotides that encode POMC peptides or polypeptides. Paterna does not teach, suggest, or even mention any specific DNA sequences that can be used to produce POMC peptides or polypeptides in a suitable mammalian cell. Paterna also does not teach, suggest, or mention any exemplary mammalian POMC amino acid sequences or any mammalian DNA segments that would encode a POMC peptide or polypeptide.

Paterna also does not teach or suggest that genetic modification of rAAV vectors by insertion of one or more mammalian POMC-encoding polynucleotides is either desirable, or advantageous for any reason. Paterna also does not provide a reasonable expectation of success, nor does it provide the requisite "blueprint" for selecting or obtaining any mammalian POMC-encoding nucleic acid segments, or for using them in the construction of genetically-modified rAAV viral vectors.

There is also no reference cited in Paterna to the prior work of Pritchard (even though the Pritchard reference pre-dates the Paterna document), suggestive of the fact that even Paterna et al. did not see the relevance of their research to the earlier work of Pritchard. Likewise, there is no suggestion or reference to the work of Paterna in the Pritchard reference. Neither reference mentions the other nor suggests that a combination of the two teachings would be beneficial,

desirable, or even plausible. Taken together or separately, there is no implicit or explicit motivation in these two references which would provide a skilled artisan with a reasonable expectation of achieving the surprising results of the present invention.

That the Paterna reference can be removed from consideration as a prior art reference altogether further illustrates the impropriety of this rejection.

2.8.4 THE ADDITION OF LASIC FAILS TO SATISFY THE LEGAL REQUIREMENTS FOR OBVIOUSNESS

The Office has also cited three additional secondary references (Lasic, Keir, and Russell) which, when taken in combination with Pritchard and Paterna, allegedly further fulfill the statutory requirement for legal obviousness of the claimed invention.

Applicants respectfully traverse.

As noted above, neither the Pritchard or Paterna references provides the requisite suggestion or the motivation to combine its teaching for the preparation of rAAV-based POMC-expressing genetic constructs that are operably linked to a promoter sequence that expresses the POMC construct in mammalian host cells that comprise such vectors.

Moreover, neither of the primary references provides the requisite suggestion or the motivation to combine its teaching for the preparation of rAAV-based POMC-expressing genetic constructs that are operably linked to a modified CMV enhancer or a β-actin promoter sequence that expresses a DNA sequence that encodes a mammalian POMC polypeptide.

The addition of the secondary references also fails to obviate the claimed invention.

On page 8 of the Action, Lasic is said to teach the use of a liposome or microsphere as a further method of delivery. The Office considers that one of skill in the art would have been

motivated to "combine the POMC peptide of Pritchard et al. and the adeno-associated viral vector of Paterna et al. with a liposome or microsphere of Lasic because Lasic et (*sic*) teaches the use of the liposome as a means to successfully package and deliver bioactive compounds."

Applicants respectfully disagree.

First, the Office has rejected claims under this combination of references (Pritchard, Paterna, and Lasic) which do not even *claim* liposomes or microspheres. Although claims 1-9, 21, 26, and 27 are rejected by this combination of references, only claims 8, 9 specifically include language encompassing liposomes or microspheres.

Even with respect to claims 8 and 9, however, the secondary reference is still deficient. Lasic contains no motivation to combine its teachings with Paterna or Pritchard (either alone or in combination) to formulate rAAV vectors, or to package recombinant adeno-associated viral particles, or to use microspheres or liposomes to formulate compositions for delivery of such viral-based vectors to mammalian host cells. Again, the required elements of this combination of references are lacking, and the rejection fails the tests for legal obviousness as outlined by the Courts as cited herein.

Applicants respectfully request, therefore, that the rejection be withdrawn.

2.8.5 THE ADDITION OF KEIR ALSO FAILS TO SATISFY THE LEGAL REQUIREMENTS FOR OBVIOUSNESS

On page 9 of the Action, Keir is said to teach the use of a microinjected rAAV vectors to target rat hypothalamus for transfection. The Office considers that, although "Pritchard and Paterna do not teach the use of the composition formulated for intracerebroventricular administration to the mammalian hypothalamus" one of skill in the art would somehow have been motivated to combine

the disparate teachings of Pritchard et al. and Paterna et al. and Keir et al to render claims 1-7, 11, 12, 21-24, 26-28, and 30.

Again, Applicants respectfully disagree.

First, the Office has rejected claims under this combination of references (Pritchard, Paterna, and Keir) which do not even *claim* intracerebroventricular administration or delivery to the hypothalamus. Although claims 1-7, 11, 12, 21, 26-28, and 30 are rejected by this combination of references, only claims 22 and 23 specifically include language concerning intracerebroventricular administration.

Even with respect to claims 22 and 23, however, the secondary reference of Keir is still deficient. Keir contains no motivation to combine its teachings with Paterna or Pritchard (either alone or in combination) to formulate rAAV vectors, or to package recombinant adeno-associated viral particles, or to use intracerebroventricular formulations, or to target the hypothalamus arcuate nucleus using intracerebroventricular administration for delivery of rAAV vector compositions that comprise a DNA sequence that encodes a POMC peptide or polypeptide. As in the case of Lasic, again the required elements of this combination of references are lacking, and the rejection fails the tests for legal obviousness.

Applicants respectfully request, therefore, that the rejection be withdrawn.

2.8.6 THE ADDITION OF RUSSELL SIMILARLY FAILS TO SATISFY THE LEGAL REQUIREMENTS FOR OBVIOUSNESS

On page 11 of the Action, Russell is said to teach "the use of microinjected rAAV vectors or virions encapsulated in liposomes into rat brains in vivo for transfection and expression (columns 9 (*sic*), lines 3-16, columns 26-27, lines 59-15). The Office considers that, although "Pritchard and

Paterna do not teach the use of the composition encapsulated in a liposome formulated for microinjected intracerebroventricular administration to the mammalian hypothalamus comprised within an isolated host cell" one of skill in the art would somehow have been motivated to combine the disparate teachings of Pritchard, and Paterna, and Russell to render claims 1-8, 11, 12, 21-24, 26-28, and 30.

Again, Applicants respectfully disagree.

The Office has rejected claims under this combination of references (Pritchard, Paterna, and Russell) for reasons which are unclear to Applicants. First, the cited portion of Russell (column 9 lines 3-16) reads as follows:

> "....lial cells were most efficiently transduced (Alexander et al., supra, 1996). Variable transduction rates have also been observed in vitro. In the case of human fibroblasts, for example, AAV2 vectors preferentially transduce S phase cells as compared to quiescent cells (Russell et al., Proc. Natl. Acad. Sci., USA 91:8915-8919 (1994) which is incorporated herein by reference), and immortalized cells as compared to normal cells (Halbert et al., J. Virol. 69:1473-1479 (1995), which is incorporated herein by reference). In contrast, hematopoietic cells including primary hematopoetic progenitors require MOI's of 1 x 10^7 or more vector particles per cell to detect transgene expression, an MOI four logs higher than that required to transduce HeLa cells (Bertran et al, J. Virol. 70:6759-6766 (1996);)."

Applicants fail to see where this passage is at all relevant to any of the rejected claims.

The second passage cited by the Office from Russell (columns 26-27, lines 59-15) notes various means of administration and various cell types and polynucleotides comprised in AAV vectors, but the reference does not suggest or provide any motivation to combine its teachings with respect to the primary references Paterna and Pritchard. The passage, which reads as follows:

> "Where an AAV viral vector is introduced into an individual in vivo, the vector can be administered systemically or locally. For example, hepatocytes in rat liver targeted by direct injection or by intravenous injection of AAV viral vectors were transduced to similar levels and expressed human clotting factor IX, which was encoded by the vector (Koeberl et al., supra, 1997). In addition AAV viral vectors containing a heterologous nucleic acid molecule encoding CFTR, which is defective in cystic fibrosis patients were administered directly to the lung using a fiber optic

> bronchoscope and CFTR RNA and protein remained detectable in airway epithelium six months after administration (Flotte et al., supra., 1993). AAV viral vectors have also efficiently transduced muscle cells following injection into mouse viral vectors encoding tyrosine hydroxylase were administered by stereotactic microinjection into rat brain and tyrosine kinase hydroxylase expression persisted for at least four months (Kaplitt et al., Nat. Genet. 8:148-154 (1994), which is incorporated herein by reference). These results indicate that AAV viral vectors can be useful for introducing a heterologous nucleic acid sequence into a cell in vivo, such that the product encoded by the heterologous nucleic acid sequence is expressed."

is silent with respect to utilization of POMC polypeptides, or the genetic engineering of recombinant AAV vectors that comprise a POMC-encoding polynucleotide. There is no motivation to combine these three references; there is not even a suggestion of modifying the references; there is certainly no expectation of success in the combination to render obvious the claimed invention.

Thus, as mentioned in the cases of the combinations with Lasic or Keir above, again the required elements for proper combination of these three references is lacking, and this rejection fails the tests for legal obviousness.

Applicants respectfully request, therefore, that the rejection be withdrawn.

2.8.7 THE CLAIMS DISTINGUISH OVER THE CITED PRIOR ART

The present inventors have shown that the claimed compositions and viral constructs are useful in methods for transfecting mammalian host cells, for producing functional POMC protein in transformed mammalian cells both *in vitro* and also *in vivo*, and for providing sustained expression of biologically-active amounts of POMC polypeptide in the host cells of an animal..

Therefore, because the claims in the case particularly point out the distinct features of the inventive methods disclosed in the Specification, and because each of such claims is clearly distinguished over the previously cited art (either alone or in combination) Applicant further believes that, as a matter of law, the rejection advanced under 35 U. S. C. § 103 cannot stand.

As reiterated herein throughout, Applicants urge the application of the standard held in the case of *In re Vaeck*, 20 U.S.P.Q. 1438 (Fed. Cir. 1991), in which the Federal Circuit stated that in order for an examiner to make out a *prima facie* case of obviousness two things must be shown:

(1) That the prior art would have suggested to those of ordinary skill in the art that they should make the claimed invention; and

(2) That the prior art must demonstrate a reasonable expectation of success of the invention.

Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the Applicant's disclosure (emphasis added).

Furthermore, in the case of *In re* Dow Chemical Co. (837 F. 2d 469, 5, U.S.P.Q.2d 1529, Fed. Cir. 1988) the court held that an "obvious-to-experiment" standard is not an acceptable alternative for obviousness, and that there must be a reason or suggestion in the art, *other than* the knowledge learned from the Applicant's disclosure.

Furthermore, the Applicant submits that *the combination of references relied upon by the Examiner also clearly fails to satisfy the tripartite test of* In re O'Farrell (7 U.S.P.Q.2d 1673, 1680, Fed. Cir. 1988). In *O'Farrell*, the Court held that in order for a reference or references to obviate an invention, it must be shown that the reference(s) contains:

(1) Detailed enabling methodology for practicing the claimed invention;

(2) A suggestion for modifying the prior art to practice the claimed invention; and

(3) Evidence suggesting that the invention would be successful.

In the present case (1) none of these references provides any teaching relevant to the question of how one of skill would proceed to prepare rAAV vector-based polynucleotide

compositions that comprise a nucleotide sequence encoding a mammalian POMC polypeptide, and most certainly does not provide any "detailed enabling methodology" for practicing the claimed invention; (2) none of the cited references in the present case provides any suggestion for combining the teachings of the individual references or for modifying any or all of the cited prior art references in a manner that would allow one to arrive at the present invention; and (3) none of the references provides evidence that the present invention would be successful. Clearly the rejections advanced under §103 in the present case are all improper as each of them clearly fails the tripartite test as mandated in *In re O'Farrell.*

In the instant case, however, there is neither the suggestion nor the reasonable expectation of success. Even if one could somehow postulate that one or more of the cited references might suggest that rAAV vectors, virus particles, host cells and compositions similar to the disclosed invention might, in an abstract sense, be *plausible*, there is certainly no teaching or suggestion as to how one would go about developing the particular rAAV-POMC vector constructs of the present invention, nor is there any suggestion in the cited references, either alone or in combination, that such an approach would be desirable or successful. Moreover, these references either alone or in any combination certainly do *not* provide the motivation for preparing the disclosed AAV vector-based polynucleotide compositions that comprise a nucleotide sequence operably linked to a CMV enhancer and a β-actin promoter sequence that encodes a mammalian POMC polypeptide. Likewise there is no motivation or teaching that such compositions, viruses, or transformed cells expressing such rAAV-POMC constructs would be useful to achieve expression in the arcuate nucleus of a mammalian hypothalamus, nor would they be able to produce a therapeutically-effective level of POMC protein when provided to an animal, or would they be sufficient for achieving the therapeutic methods also set forth in the

present Specification. Likewise, there is no suggestion or expectation that such rAAV-POMC compositions, host cells, and kits, would or could be utilized in any methods for the treatment, prevention, and or amelioration of symptoms of one or more diseases caused by a deficiency in POMC protein in an animal, and in particular, there is no suggestion or expectation of success in using such compositions in the therapy of mammals (including for example, humans) that have, are diagnosed with, or are at risk for developing one or more conditions such as polyphagia, hyperinsulinemia, adiposity, an eating disorder, or excessive body weight gain.

Applicant asserts that any combination of the cited references is, at best, merely an invitation for further experimentation in the field, and at most, an "obvious-to-try" situation. However, there is *no* reasonable expectation of success, *nor* is there the motivation or teaching to guide a skilled artisan how to achieve such success. The Federal Circuit, in the case of *In re Geiger* (815 F.2d. 686, 2 U.S.P.Q.2d 1276, Fed. Cir. 1987), held that obviousness cannot be established by combining the teachings of the prior art to produce a claimed invention, absent some teaching, suggestion or incentive supporting the combination. Again, Applicant believes that each of the "obviousness" rejections advanced in the present case fails the test of *In re Geiger.*

Further, in *Amgen v. Chugai Pharmaceutical Co. Ltd.*, (927 F. 2d 1200, 18 U.S.P.Q. 2d 1016, 1022, Fed. Cir. 1991) the Court affirmed that obviousness under 35 U. S. C. § 103 is a question of law, and that both the suggestion and the expectation of success must be founded in the prior art, and not in the Applicant's disclosure. Because the suggestion and expectation of success are absent in the cited art, Applicant asserts that each of the §103 rejections also fails the test of *Amgen v. Chugai Pharmaceutical Co. Ltd.*

For these reasons, Applicants respectfully request that each of the obviousness rejections be withdrawn because each fails to meet the requirements for legal obviousness under 35 U. S. C. § 103(a).

2.9 REQUEST FOR EXAMINER INTERVIEW

Pursuant to M. P. E. P. § 713.01 and 37 C. F. R. §1.133, should any claims remain objected to, or rejected under any section of the Statutes, or should any issues remain in the mind of Examiner Salvoza after entry of the present amendment and consideration of the remarks herein, a telephone call to the undersigned Applicants' representative is earnestly solicited within 30 days' receipt and initial consideration of the present paper for the purpose of scheduling an Examiner Interview. Applicants herein specifically request that should any claims remain rejected in the mind of the Examiner upon consideration of the amendment and remarks herein, that the undersigned agent be contacted to arrange such an interview in a timely fashion prior to the issuance of a further Action on the merits in order that all parties can mutually agree on a time and place in which to conduct the interview.

Should no issues remain outstanding after consideration of the amendment and remarks herein, however, and should all pending claims be found allowable, Applicants state their intent to waive this request for an Examiner Interview upon receipt of a Notice of Allowance for all pending claims.

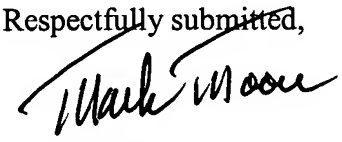
2.10 CONCLUSION

It is respectfully submitted that all claims are fully enabled by the Specification, are definite, and are free from rejection over any or all of the cited prior art. Applicants believe that

the claims are acceptable under all sections of the Statutes, and that all previous concerns of the Examiner have been resolved. Applicants further respectfully request, therefore, the withdrawal of all rejections and that a Notice of Allowance be issued in the case with all due speed. However, Applicants also note for the record their explicit right to re-file claims to one or more aspects of the invention as originally claimed in one or more continuing application(s) retaining the priority claim from the present and parent cases.

Should the Examiner have any questions, a telephone call to the undersigned Applicants' representative would be appreciated.

Respectfully submitted,



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